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ENVIRONMENTAL TOBACCO SMOKE AND CORONARY HEART DISEASE

A.K. Armitage
Consultant Pharmacologist and Toxicologist, Knaresborough, UK

Abstract

The possibility that exposure to environmental tobacco smoke (ETS) may increase the risk of non-smokers developing coronary heart disease (CHD) is a matter of debate. The results of published epidemiology studies have been considered according to the classical criteria for judgment of causality. Twelve epidemiological studies have been published on the alleged relationship between exposure to ETS and the risk of CHD in non-smokers. The relative risks generally fall between 1 and 2, which represents a 'weak association'. Although the reported association shows some signs of consistency, it is not strong, nor it is specific. The lack of consistency between dosimetry and epidemiology casts doubt on the biological plausibility; further claims of a dose/response relationship, which are based entirely on reported cigarette usage, are not wholly convincing. On current evidence a causal relationship between exposure to ETS and the development of CHD has not been proved.

Key words: Environmental tobacco smoke (ETS), coronary heart disease (CHD), association and causality, dosimetry, publication bias, biological plausibility

Introduction

The debate regarding the association between smoking and cardiovascular diseases, especially coronary heart disease (CHD) has, during recent years, led to consideration of the possibility that exposure of non-smokers to environmental tobacco smoke (ETS) might increase the risk of such disease. The uncertainty about the existence of such an association is evident from the pronouncements of groups of scientists who carefully and critically reviewed the relevant data available at the time of their review.

1986: US Surgeon General [1] – "Further studies on the relationship between involuntary smoking and cardiovascular disease are needed in order to determine whether involuntary smoking increases the risk of cardiovascular disease". This view was based on four studies which had been published at that time.

1986: National Research Council [2] – "With respect to chronic cardiovascular morbidity and mortality, although biologically plausible, there is no evidence of statistically significant effects due to ETS exposure, apart from the study of Hirayama in Japan" (four studies considered, three of which were also considered by the US Surgeon General).

1990: Environmental Tobacco Smoke – Proceedings of the International Symposium at McGill University, Montreal [3] – Dr Wexler and discussants unanimously concluded that the data from seven studies would not provide any basis for altering the Surgeon General's and the National Research Council's conclusions concerning ETS and cardiovascular disease.

Address correspondence to Dr A.K. Armitage, Sycamore Lodge, Abbey Road, Knaresborough, North Yorkshire HG5 8HX, UK. *(Accepted for publication 30.7.92.)*

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1990: Lin™ ks between passive smoking and disease: a best-evidence synthesis [4] – This report of an 11-member working group on passive smoking stated in 1990 that "after an initial review of the literature, we determined that insufficient studies of high quality had been done in the area of cardiovascular disease to warrant comment in our review at the present time".

Most of the studies upon which these opinions were based were not designed specifically to investigate the effects of ETS exposure on CHD. According to Weetman & Munby [5] they were later adapted to this purpose after the initial claims that ETS affected health adversely had appeared in 1981–1982. Thus, neither of the two large prospective studies [6,7] was conducted according to accepted principles, i.e. systematic collection of risk factor data at intervals and complete follow-up of all deaths. With the exception of the recent study of Dobson and associates [8], it is notable that all the other published studies involved only very small numbers of deaths [9].

Epidemiology data and the question of causality

Twelve epidemiology studies have now been published ([6–8,10–20] – see Table 1) on which to base a judgement but few details were provided for two of the case-control studies and the studies of Martin *et al.* [11], Palmer *et al.* [13] and Butler [19] have only been published as abstracts; full papers are still awaited. Some of the data in the Table are based on figures quoted by Lee [21] and Glantz & Parmley [22]. In attempting to interpret the results of these studies it is appropriate to recall the elements of evidence laid down by the United States Surgeon General [23] and the late Sir Austin Bradford Hill [24] that need to be considered before a reasonable inference of causation for studies that purport to show association can be made. Hill's elements were as follows:

- an association should be strong
- it should be consistent across a variety of subjects and circumstances
- it should be specific
- exposure must precede the observed outcome
- there should be a dose-response relationship
- the association should be biologically plausible
- evidence from all relevant scientific disciplines should be coherent
- experimental evidence should be sought whenever possible
- analogy to similar cause and effect relationships should be considered.

Hill's criteria did not actually include – "sources of bias must be excluded" – though it is implicit in the condition – "an association should be strong". Sources of bias and confounders, which feature so prominently in all papers concerned with the association of ETS and the development of disease are, therefore, logically considered under strength of association.

The United States Surgeon General [23] wisely commented in 1964 that "Statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgement which goes beyond any statement of statistical probability". It is regrettable, however, that three decades on judgements tend to get clouded to fit in with beliefs. Each of Hill's elements will be considered in turn.

Strength of association

The possibility of an association between CHD and alleged exposure to ETS has arisen from observational studies (prospective and retrospective) of groups considered to be either exposed or not exposed to ETS. Risk of death from CHD in the exposed group relative to the unexposed group is calculated by application of appropriate statistical techniques.

There are considerable difficulties in conducting and interpreting epidemiology studies when the 'increased risk' is small. Indeed, it has been stated [25–28] that epidemiology cannot usually reliably predict relative risks of less than two.

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Table 1. Epidemiological studies of environmental tobacco smoke (ETS) and coronary heart disease (CHD).

Reference	Location	Sex	CHD deaths or cases		Relative risk	95% conf. limits	Factors adjusted for
			Unexposed	Exposed			
Case control studies:							
Lee *et al.* [10]	UK	M	26	15	1.34	0.64–2.80	None
		F	22	55	.97	0.56–1.69	
Martin *et al.* [11]	US	F		23'	2.6	1.2–5.7	Not known
He [12]	China	F	9	25	1.5	Unknown	Age, race, residence, occupation, hypertension, family history of hypertension or CHD, alcohol, exercise, hypercholesterolaemia
Palmer *et al.* [13]	USA	F		7'	1.2	Unknown	Not known
Dobson *et al.* [8]	Australia	M	161	22	0.97	0.50–1.86	Age and history of myocardial infarction
		F	117	43	2.46	1.47–4.13	
Prospective studies:							
*Hole *et al.* [15]	UK	M+ F	30	54	2.01	1.21–3.35	Age, sex, class, blood pressure, cholesterol, body mass
Svendsen *et al.* [16]	US	M	8	5	2.23	0.72–6.92	Age, blood pressure, cholesterol, weight, education, drinks
**Helsing *et al.* [6]	US	M	248	122	1.31	1.05–1.64	Age, marital status, schooling, housing
		F	437	551	1.19	1.04–1.36	
Hirayama [7]	Japan	F	118	376	1.15	0.94–1.42	Age
Garland *et al.* [17]	US	F	2	17	2.7	0.90–13.6	Age
Humble *et al.* [18]	US	F		76'	1.59	0.99–2.57	Age, cholesterol, blood pressure, body mass
Butler [19]	US	F		64'	1.4	0.50–3.80	Age

* Hole *et al.* is an update of Gillis *et al.* [14], but is not a separate study
**Helsing data extracted from later paper by Sandler *et al.* [20]
'= total number of cases

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The 12 studies provided 15 different estimates of relative risk for either men or women, and 95% confidence intervals are available for all but two of these. Table 1 shows that 13 out of 15 indicate a relative risk of >1 but eight of these have a lower confidence limit of <1, indicative of a non-significant effect. Although the studies suggest an association, because most of the claimed relative risks lie between one and two, Hill's criterion of strength is not satisfied.

The studies by Butler [19], Dobson *et al.* [8] and Svendsen *et al.* [16] give some data on ETS exposure at home, work, leisure and travel situations. *None* of these supplementary results was statistically significant.

Meta-analysis

Recently the results of all studies have been combined using the technique of meta-analysis [29,22]. Wells [29], using studies available in 1987, computed a pooled relative risk of 1.3 (95% confidence interval, 1.1–1.6) for men and 1.2 (95% confidence interval, 1.1–1.4) for women. Glantz & Parmley [22] reported a relative risk of 1.3 (95% confidence interval, 1.2–1.4) for men and women combined.

Meta-analysis is a mathematical technique primarily developed for handling data from multi-centre randomised clinical trials where the same protocol for the selection of patients, the selection of control subjects, dosing and observation is followed in each of the collaborating centres. Whether such techniques are scientifically appropriate for epidemiological studies conducted in different countries by investigators using widely different methods and criteria is doubtful [30–34].

Meta-analysis does not increase the *strength* of the association, although by reason of narrowing the 95% confidence intervals it may produce a mathematically, though not necessarily biologically, significant relative risk. The Glantz and Parmley paper [22] has recently aroused criticism and debate [35–38] on a number of issues including the mathematical model used by Wells [29].

Misclassification bias

According to Lee [39,40] most, if not all, of the apparently higher risk of lung cancer among non-smoking women married to smokers compared to non-smoking women married to non-smokers can be explained by a bias introduced when smoking (or ex-smoking) women claim untruthfully to be non-smokers. Such misclassification leads not only to imprecision but to *bias*, because smokers tend to marry smokers and non-smokers tend to marry non-smokers more than would be expected by chance. Misclassification bias of this kind affects not only the interpretation of data relevant to lung cancer risk from ETS but also to some extent that relevant to CHD risk [21]. The matter of smoking habit concordance has been fully discussed by Lee [21].

Publication bias

Lee [21] has shown that there is a tendency for the studies with small numbers of deaths or cases to have the largest relative risk estimates. For example, Table 1 shows that the highest relative risk reported, i.e. 2.7 by Garland *et al.* [17] was based on only 19 deaths, whereas one of the lowest relative risks (1.19) reported by Helsing [6] was based on 1,358 deaths in the largest of the 12 studies. Lee [21] suggests that this is a manifestation of publication bias. He also points out that the American Cancer Society has relevant data on many thousands of deaths from heart disease among women who have never smoked, but has not so far reported results which, according to Lee, suggests that no relationship with ETS was found. The possibility of publication bias has been strengthened by the paper of Easterbrook *et al.* [41] which states, "we have confirmed the presence of a systematic selection bias in the publication process according to study results. Studies with a statistically significant result for the main outcome of interest were more likely to be submitted for publication and more likely to be published than studies with null results, after adjustment for confounding factors". Thus, conclusions of meta-analyses based only on published work may produce a misleading high estimate of relative risk.

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Other potential confounders

Neither of the two large studies [6,7] recorded details of major risk factors for CHD such as blood pressure, blood cholesterol levels, obesity, etc, an omission criticised by a number of reviewers [3,5,21]. In the studies by Helsing/Sandler [6,20] and by Hole [15] the index of ETS exposure was based on living with a smoker, but no adjustment was made for the number of people in the household. Since household size may correlate with various facets of disease, adjustment should have been made for it in the analysis. Dobson *et al.* [8] collected data on smoking behaviour for cases and controls by different methods and showed that, for the controls, smoking frequency varied according to the location of data collection. This provides a further important example of potential bias.

Consistency of association

Statistically, assuming no systematic bias, it would appear unlikely that 13 out of 15 estimates of relative risk >1 could have arisen by chance. Although some element of consistency amongst the published studies is indicated the possibility of publication bias may have accentuated the consistency of the association.

Specificity of association

There are two distinct aspects of specificity – one relating to the exposure and one to the disease. CHD is a common cause of death in non-smokers, which is hardly surprising when almost *300* so-called risk factors have been described [42] and the literature on such risk factors "seems to expand at almost exponential rates" [43]. For this reason, the cause of CHD is frequently stated to be multifactorial in origin. It has been said that "the phrase is a synonym for 'unknown' and thus a euphemism for ignorance" [44]. CHD is of course not the only disease to be linked with ETS. There is, therefore, an absence of specificity in the association, as Wexler [3] also concluded.

Temporality

Hill [24] stressed the need to consider the temporal relationship of any association, particularly for diseases of slow development. There are no data available on which to address the importance of the temporality of the association between ETS and CHD. In view of the multi-factorial nature of the disease, which inevitably complicates its precise development, it is doubtful if there ever will be any unequivocal data in this context.

Dose/response relationship

Exposure

ETS is a mixture of sidestream tobacco smoke (the smoke that originates from the smouldering end of a cigarette, cigar or a pipe between puffs), waste mainstream smoke (i.e. that expelled prior to inhalation) and exhaled mainstream smoke diluted with variable but much larger volumes of ambient air. Additional physical and chemical changes occur as the mixture ages. The concentration and nature of ETS to which an individual is exposed depends, among other things, on:

- type and number of cigarettes smoked in a given time
- volume of room
- ventilation rate
- proximity of burning cigarette.

The effective daily dose for any exposed individual depends upon the concentration in various environments and the time spent in these environments, which highlights the difficulty of assessing exposure under 'real life' conditions [45]. Additionally, exposure must relate to a time-span that is appropriate to the development of the disease.

ETS is a complex mix of many components and, because no known substance is representative of all of these, it is not possible to monitor ETS exposure meaningfully [5]. Nicotine comes closest to fulfilling some of the requirements for a suitable marker [46]. Kirk *et al.* [47] measured atmospheric nicotine, carbon monoxide and particulate matter in nearly 3,000 locations over 30 minute periods in travel, work, home and leisure situations. Their data show that levels vary greatly both within, and between, situations. They illustrate how inadequate and misleading is

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an assessment of ETS exposure in epidemiology studies based merely on reported smoking habits of couples living together, determined from questionnaires.

The reliability of questionnaires represents a weakness of all experimentall designs, particularly when smoking spouses themselves were not always questioned [48]. Additionally, some are untruthfull about their smoking status and misclassification of non-smokers who are really smokers invariably results [39,40]. In the large Helsing study [6], the only smoking data that were collected on every person was in 1963, and no attempt was made to see whether changes in smoking habits occurred during the study.

Dosimetry

Dosimetry assessment involves the measurement of a substance in biological fluids. If ETS has any affect whatsoever on CHD then the only reasonable way that this could come about is by absorption of a component or components of ETS into the systemic circulation. No such measurements have been incorporated in any epidemiological study.

As with markers of exposure, there is no single substance that is reliably representative of ETS. Both nicotine and carbon monoxide have been implicated in possible mechanisms by which active cigarette smoking may accelerate the development of CHD [49]. Nicotine and its metabolite cotinine, which has a half-life of 15–20 hours, have been measured in: (a) ETS exposed non-smokers, (b) non-smokers not exposed to ETS, (c) active smokers [50]. Very small amounts of cotinine are found in the plasma, saliva and urine of non-smokers. Whilst non-smokers allegedly exposed to ETS are reported to have higher cotinine levels than non-smokers not exposed, these levels are minute compared with those found in active smokers (about 1/300) and variation between subjects is large (up to 10-fold).

In non-smokers, endogenous production of carbon monoxide results in low blood levels of carboxyhaemoglobin (COHb) in the range 0.5–1.5% [51]. Small increases of COHb due to ETS exposure may be indistinguishable from those due to endogenous production and non-tobacco related sources [1].

Clearly, the amounts of nicotine and carbon monoxide absorbed from ETS are small and it is unlikely that either compound plays any role in the alleged increased relative risk for CHD of non-smokers exposed to ETS. It would be surprising if any other smoke component was absorbed in significant amounts from ETS.

Dose/response

Some authors [7,12,15,16] of the studies listed in Table 1 claim that their data demonstrate a dose-response relationship between ETS exposure (based on the number of cigarettes smoked by the active smoking partner) and death from CHD. In view of the imprecision of such dosage assessment, these claims should be viewed with caution [52].

Biological plausibility

Although ETS is a different entity from mainstream smoke, it contains many of the same components, and attempts have been made to equate ETS exposure with active smoking in terms of 'cigarette equivalents'. On such exposure/dosimetry considerations, the relative risks of more than two reported in some ETS studies [8,11,15,16,17] are implausibly high, set against the reported relative risk for active smoking of 1.9 in males and 1.8 in females [53]. Professor Wald concedes that the association seems "surprisingly large" and requires explanation [54] and has commented that the risk of 1.3 given by Glantz & Parmley [22] is "too high to be biologically plausible" [55].

That one author [17] can incorrectly report a relative risk of 14.9 (the major finding of the study) and then subsequently 'correct' it to 2.7 whilst maintaining that this "does not affect the conclusions" [56], casts grave doubt on the conduct of the whole study. Likewise, when Hirayama [57] reported on the first 14 years of his prospective study, there was no mention of a higher mortality rate from CHD of non-smoking women married to smokers. Armitage [45] pointed out that "it is difficult to believe that a

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previously unsuspected risk could become apparent merely as a consequence of three more years of follow-up". Doll [58] has commented that if you find something unexpected but of social significance you have a responsibility to be sure that you are right before you publicise your results to the world. In the same paper he also offered additional advice that ". . . as a research worker, you always ought to try to disprove your own findings".

Pipe smoking

Pipe smokers inhale tobacco smoke both actively (to an extent) and passively. They surround themselves in dense clouds of tobacco smoke and are regularly exposed to high concentrations of ETS, yet experience "little if any excess risk of death from coronary heart disease" [59]. It is unlikely that the chemical composition of pipe sidestream smoke would differ appreciably from that of cigarette sidestream smoke. Therefore, these observations provide suggestive evidence against a role of ETS as a cause of death from CHD.

Coherence

This criterion addresses the effects of ETS on biological systems which have been claimed to support a causative hypothesis.

Platelet function

Glantz & Parmley [22] claimed that ETS adversely affects platelet function in a way that increases the risk of heart disease. This conclusion is not warranted considering that the study cited [60] measured a response to an ETS insult in non-smokers kept together in an 18m² room for 20 minutes, while testers smoked "30 heavy brand" cigarettes. The relevance of these 'artificial' experiments to CHD problems is questionable. It is not known whether, under normal conditions of ETS exposure encountered in real-life situations, the platelet function of non-smokers exposed to ETS differs from the platelet function of non-smokers not so exposed.

Fibrinogen levels and thrombogenesis

Dobson and associates [8] reported plasma fibrinogen concentrations in the control subjects of their case-control study in an attempt to provide mechanistic support to their conclusion that exposure to ETS in the home increases the risk of fatal and non-fatal heart attack. The authors state that "people exposed to passive smoking had higher levels than those not exposed (except for passive smoking at home for women)". However, the results were not significant and the workplace means for non-smoking men and women (exposed *vs.* non-exposed) were virtually the same.

Effects of ETS/carbon monoxide on exercise tolerance

Healthy people can inhale enough carbon monoxide to reduce the oxygen carrying capacity of the blood by 10% or more, without ill-effect [61]. However, people with reduced circulatory efficiency (e.g. because of existing heart disease) may be temporarily compromised by exposure to carbon monoxide; their exercise tolerance may be reduced and they may develop anginal pain sooner than in the absence of carbon monoxide. Aronow [62] reported a reduction in the duration of exercise until the onset of pain in 10 patients exposed to ETS, which resulted in mean COHb levels of 1.77% and concluded that exposure to ETS was harmful to patients with angina pectoris. Aronow's experiments were not conducted on a strict double-blind basis and the measured end-point was a subjective one. Much of his work has now been generally discredited [1,63,64]. Sheps *et al.* [65] have since shown that blood levels as high as 4% COHb have no significant effect on a range of parameters examined in patients with ischaemic heart disease. This well-controlled study casts considerable doubt on the suggestion that elevation of carbon monoxide levels in the blood resulting from ETS exposure is demonstrably harmful.

Experiment

Hill [24] asked whether the frequency of the associated event (CHD death) was affected by preventative action (modifying ETS exposure). No data relevant to this question are currently available. Whether it would be possible to design a sufficiently sensitive

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study to demonstrate objectively the value of preventative action in any specific situation seems questionable.

Analogy

ETS is one of the many problematical materials on which toxicologists have had to make safety evaluation judgements because of its variable composition and complex physico-chemical properties. The obvious analogy is with mainstream tobacco smoke to which reference has been made in the section on biological plausibility. Great caution, however, needs to be exercised in making judgements in this context [52].

Conclusion

The case for ETS exposure causing CHD is wholly unconvincing because almost all of the accepted 'causational' criteria remain unsatisfied. Of particular concern is the weakness of the association, the likelihood of the existence of publication bias resulting in an overestimate of a very low relative risk, the lack of biological plausibility and the anecdotal nature of dosimetry assessment.

At the present time, therefore, one is not able to conclude categorically that ETS is, or is not, harmful in a cardiovascular context. It is debatable whether the conduct of further epidemiological studies, frequently recommended, is practical and justified. Small studies are a waste of time and money because at best they can only detect large risks as significant. Of course it is *theoretically* possible to conduct a prospective study, as envisaged by Wexler [3], which would control for all confounding variables and involve a sufficient number of subjects to provide reasonable statistical power. However, even large studies cannot distinguish with any certainty between a very low risk and no risk. Furthermore, without meaningful measurement of prolonged ETS exposure, results might still be inconclusive regarding the question of causation. In the meantime, it is wrong that an ETS/CHD health scare has been blown up out of all proportion in the last few years by a passionate anti-ETS health lobby. Interpretive opinions are not proven facts; they must be challenged and a more balanced point of view presented to the general public.

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